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THE WONDER DRUGS

An NBC Radio Discussion by WALSH McDERMOTT
C. PHILLIP MILLER *and* JOSEPH E. SMADEL

Including

Some Observations on the Development of Resistance to Antibiotics

By C. PHILLIP MILLER

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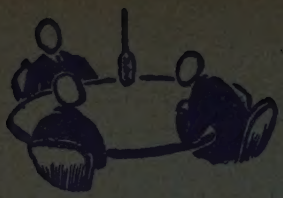

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Some Observations on the Development of Resistance to Antibiotics. *By* C. PHILLIP MILLER 1

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The Wonder Drugs

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DR. MILLER: Every listener to this program today has heard and read bout the wonder drugs—what we doctors call "antibiotics." Actually nese drugs are almost as wonderful as enthusiastic newspaper and nagazine writers would have us believe.

Only a few years ago such diseases as pneumonia, meningitis, typhoid ever, and epidemic typhus were dreaded by patient and doctor alike. Today, treatment with penicillin, streptomycin, aureomycin, and chloro-nycetin has eliminated them as serious threats to the patient. Medicine oday is truly in a golden age of the treatment of infection.

What are the antibiotics? What diseases do they cure? Technically peaking, an antibiotic is a substance produced by a living organism vhich markedly affects the life-processes of another organism. The anti-iotics with which we are concerned, however, are those which are seful in the treatment of human disease.

Dr. Smadel, which of these miracle drugs are the most important?

DR. SMADEL: There are innumerable antibiotics, and every day scien-ific journals list new ones. But, of this entire group, there are only four vhich are really important. These are: (1) penicillin, (2) streptomycin, 3) chloromycetin, and (4) aureomycin.

DR. MILLER: Why is it that these four drugs have been chosen?

DR. MCDERMOTT: There are two principal reasons why these four have een chosen: First, as Dr. Smadel said, there are hundreds, literally, of rugs which are active against microbes in the test tube, but only a very ew of these maintain this activity when they are introduced into the uman body. The others are either broken down or neutralized or therwise changed so that they are no longer active against the bugs. The second thing is that, of the small number which do maintain activ-y within the body, many of them are too toxic for the human being, as vell as being too toxic for the bacteria. So, for those two reasons, I would ay that these four drugs—penicillin, streptomycin, chloromycetin, and ureomycin—are the only four which can be considered as established ntibiotics.

DR. MILLER: Of what use are these four antibiotics in caring for th sick? I should say that they are primarily useful in the treatment of infe tious diseases—that is, the diseases caused by microbes, in contrast wi such diseases as cancer or the degenerative diseases, such as hardenir of the arteries, heart failure, or the metabolic diseases such as diabete The infectious diseases are the diseases caused by microbes. How wou you best classify microbes?

DR. MCDERMOTT: One way that they could be classified, of course, by size. They are all small. They are all so small that they require microscope to be seen. But the largest type microbes are the microb such as the amoebae which cause dysentery or which cause malaria, certain of the fungi. In the medium-sized group could be grouped th bacteria, the spirochetes, or the rickettsia; and in the smallest grou would be the viruses of the smallest size.

DR. SMADEL: In our discussion today I think that we should lim ourselves to consideration of the agents of middle and small size—th bacteria, the spirochetes, the rickettsia, and the viruses.

Before we go any further, though, we should consider how these ant biotics work on the organisms.

DR. MILLER: They do not kill bacteria outright, such as do antisepti like iodine, or bichloride of mercury, or carbolic acid, but they act on ba teria in a much more subtle way and stop their growth.

DR. MCDERMOTT: Would it be safe to say that they check the onwar progress of the infection so that the body has an opportunity to mobiliz its own mechanisms of defense finally in order to throw off the infe tion?

DR. MILLER: That is a very good point.

DR. MCDERMOTT: Could you say, for example, that by the use of thes drugs you buy time for the body to do that? After all, individuals var as to the speed with which they can mobilize their own defense mecha nisms. In the old days with pneumococcus pneumonia, for example, on man might be able to mobilize his defenses in forty-eight hours. Anothe man might require seven or ten days. In a disease such as that, seve or ten days was too long, but with these drugs we more or less artificiall give everybody the same opportunity. We buy time for them to mobiliz their defenses. Would you agree with that?

DR. MILLER: I would agree perfectly.

DR. SMADEL: We should reemphasize, I believe, the whole matter of uppression rather than killing, because it seems to be the main mechnism by which these drugs benefit disease. One excellent example of hat is found in typhoid fever. Here we normally have a disease which uns for five or six weeks. That means that it takes about that length f time for the body to overcome the infection under normal conditions. f we treat the patient with chloromycetin, we can cure the disease in everal days. That may be done during the second week of illness. When ve do that, the patient has not had time to develop his resistance, his mmune mechanisms. Therefore, if we treat for a few days and stop the reatment, the patient is likely to develop a relapse. We found this out he hard way by observing the relapses and treating them again, but now ve know that if we treat the patient and then continue to give him the ntibiotic for a period of several weeks, until he has had time to develop is own immune response, then he does not relapse.

DR. MILLER: What types of infections are controlled by these drugs, nd which are not? I suppose that in the first category we ought to list nost of the bacterial and spirochetal diseases. For instance, pneumonia, pidemic meningitis, typhoid fever, all the venereal diseases, and such ickettsial diseases as typhus fever and scrub typhus and Rocky Mountain spotted fever.

DR. SMADEL: Those are some of the good results we get. There is one ery large group in which many of us are interested, the viruses, which re really not very well affected. There are a few of the virus diseases, articularly one of them, the viral pneumonias, which are sometimes aused by the agent psittacosis, the one which causes parrot fever. In hat instance there may be some benefit.

Another related disease, related so far as the agent itself is concerned, s a venereal disease of man. There again we have some benefit. But, by nd large, in the viral diseases we have no therapeutic agents which are f any value. That includes the diseases of childhood, such as measles, numps, chicken pox. It includes the epidemic diseases such as smallpox nd influenza, and the very common disease, the common cold.

DR. MILLER: In other words, one or the other of these drugs which we ave mentioned—penicillin, streptomycin, aureomycin, and chloromyetin—is effective in most of the diseases caused by ordinary bacteria and y the rickettsia, but not against the disease caused by the viruses.

There are some diseases which are not completely controlled but ar greatly benefited by antibiotics—in other words, are partially controlle I suppose that the most important one of these is tuberculosis. Dr. M Dermott, you are an active investigator in this field, and, as editor of th *American Review of Tuberculosis,* you are thoroughly familiar with a the most recent work on tuberculosis.

Dr. McDermott: The problem with tuberculosis really arises fro three things: First, the very chronic nature of the disease; secondly, th fact that the disease is so destructive, particularly tuberculosis of th lungs, which is the important part of the tuberculosis problem; an third, the one antibiotic, streptomycin, which is highly active again tubercular bacilli, happens to be the one drug to which the bacteri become accustomed and develop a resistance to it after a variable perio of time.

Now, so far as the chronic nature of the disease is concerned, tuberc losis is a disease of weeks or months. Really, it is a disease of months c years, in contrast to typhoid fever, which is a disease of weeks, or pneu monia, which is a disease of days.

The nature of the illness, with its long length, leads to a considerabl amount of destruction in the lung. There are areas of living tissue, dyin tissue, and dead tissue, all interlaced with scars. That presents the ver worst type of situation for the use of any antibiotic drug in any infectio for no drug can restore tissue. And then, when one adds the fact tha after a period of, let us say, two or three months, the bacteria are n longer affected by the drug—in fact, as you yourself have shown, Dr Miller, they may even thrive on the drug—you have a very difficult situa tion. I think that you might say that, in essence, we have an excellen short-term treatment for what is in effect a long-term disease. Tha short period, that armistice for two or three months, may be enough i many instances to do the trick, but in many more instances it only buy a small period of time for the patient. Eventually, when the bugs be come resistant to the drug, the patient is right back where he started That does not necessarily mean that he dies of tuberculosis, because, afte all, we have very excellent surgical and other measures for treatin tuberculosis. But it does mean that we can no longer control that particu lar infection with the antibiotic drug, streptomycin.

Dr. Smadel: There is another very good example in the urinary infec tions, those infections of the kidney and bladder, where many of th

ings hold which you have just discussed for tuberculosis. There may e chronic lesions which are dependent upon urinary stones; there may e congenital malformations which result in obstruction to urinary flow. ll those things are conducive to the growth of bacteria. Now, when ve give the antibiotics, they may be very effective for a few days, but ventually the bacteria which are causing the infection in the patient ecome resistant to the antibiotic, and the drug no longer has an effect. o, here again, in this type of infection it is important that one control t, get in at that time while there is control and remove the initial cause—ake care of the stone, take care of the obstruction, whatever it is—ecause the antibiotic itself will not cure the patient.

DR. MILLER: In other words, then, there are antibiotics which will lefinitely cure a large number of infectious diseases, and then there are liseases in which antibiotics fail to bring about a cure, but are definitely ielpful in the treatment of the disease.

What are the limiting factors in the use of these drugs?

DR. SMADEL: We have already mentioned toxicity. Every drug which we use as physicians is toxic in some respect. The only reason we use hat drug is because the therapeutic dose is below the toxic dose. The same thing is true of antibiotics. Furthermore, there are several kinds of toxicity. There is the direct, killing effect of the drug on the human cell. There is another kind, an allergic type. In general, penicillin has very little direct toxicity. It can be used in enormous doses without affecting the patient. It is ideal in that respect, in that it affects the bacteria without affecting the host. Of the other antibiotics which were mentioned and which are more important, aureomycin and chloromycetin are not very toxic for man. It is true that one may get some mild sign, such as nausea, or vomiting, or black tongue, or some odd thing like that. That really is not too important, but the one which we have mentioned, streptomycin, does have a definite toxicity which can be very disturbing. Streptomycin affects the nerve which has to do with hearing and balance of the body. Therefore, it is not unusual for patients who get too large a dose of streptomycin to develop deafness and dizziness.

Dr. McDermott, what about the allergic types of toxic reactions?

DR. MCDERMOTT: Of course, you were talking about toxicity in terms of what is, in effect, overdosage. That is, such and such a dosage would produce such and such an effect.

Of course, the allergic-type reactions do not bear a direct relationship

to dosage. People may become allergic to virtually any drug in the sam way that certain individuals are allergic to strawberries or sea food. Ver minute amounts of the drug may be sufficient to call forth an allergi reaction. In general, these allergic reactions are not particularly serious In the first place, in the acute infections, at least, they usually occur lat in the course of treatment, so that by the time the patient has the reactio he no longer requires the use of the drug. And, secondly, their manifes tations are usually mild and, in general, consist principally of such things as hives or a skin rash. That does not mean, of course, that some one might not be very uncomfortable indeed with an allergic reaction but they seldom are really very serious.

The important thing is the fact that to penicillin, for example, whe such reactions occur, they are by no means necessarily sustained in definitely. That is, in a patient who has an allergic reaction to penicilli in an infection in January, it may be entirely possible for him to tak penicillin three or four or six months later. The same holds, but to lesser degree, with streptomycin and with the other drugs.

There is a certain amount of confusion on that point, because peopl tend to mix up the allergic reactions to the drug itself and the resistanc which the bugs develop to that drug.

Dr. Miller, do you not think that there has been a fair amount o loose talk on the subject of drug resistance?

DR. MILLER: Oh, yes. That is because the development of resistance t antibiotics by bacteria is a problem which is of great theoretical interes to the bacteriologists and is of some practical importance to the physi cian. It is a phenomenon which can be readily demonstrated experimen tally in the laboratory. In the case of penicillin, bacteria do develo resistance, but they develop it slowly. In the case of streptomycin, bac teria can develop resistance very quickly. In fact, bacteria can becom not only resistant to streptomycin but they can become dependent on it That is to say, they change in such a way that they actually require strep tomycin for their growth. Fortunately, these streptomycin-requirin bacteria are of no serious importance in the treatment of disease, but, a you have indicated, Dr. McDermott, the streptomycin-resistant bacteri may complicate the treatment of diseases which require streptomycin fo their treatment.

DR. MCDERMOTT: Would you say it was safe to say that drug resistanc

only a problem really at the clinical level with streptomycin therapy nd that it is not with penicillin?

DR. MILLER: Nor with aureomycin or chloromycetin. Quite right. The question has arisen whether the continued use of these drugs by ie whole population may give rise to the gradual increase in resistance whole categories of bacteria, as happened, for instance, in the case of ie sulfonamide drugs in the treatment of gonorrhea. I think, personlly, that this fear is very much overrated. One cannot tell. In the course f many years, it is quite possible that bacteria will acquire some resistnce to the drugs, but I do not think that we need to worry about that or a long time to come.

DR. SMADEL: It is a very good point, since we are talking about public ealth and preventive medicine, to bring in the whole relation of antiiotics to preventive medicine. Of course, our listeners are familiar with he fact that, in preventive medicine, the physician is interested in elimiating the infectious agent so that the patient never comes in contact vith it; or if that is impossible and if the patient must come in contact vith the agent, then the idea is to increase the individual's resistance so hat he is immune. The general objectives, then, of preventive medicine re considerably different from those of therapy, which is concerned vith treatment of the patient.

But there are certain instances in which the antibiotics and these new nethods of treatment do bear on preventive medicine. One of those roblems has to do with immunization. In the past there were a number f diseases which were so severe that we, as physicians, have advised that he individual be immunized against them, even though his chance of ecoming infected from exposure is very, very slight. Several examples f those are typhoid fever and Rocky Mountain spotted fever. Even hough one's chance of getting these diseases was one in a million, if he ot the disease, he was certain to be sick for a long time and he might ven die. Therefore, we could not take a chance and had to recommend mmunization. Now that we have good therapeutic measures for these nfections, we can afford to take this one-in-a-million chance, and there re a number of instances then in which we can say to the individual hat it is not necessary to be immunized. Now I would like to make it ery clear, though, that these are specific instances and that, in general, he immunization procedures which are now used are required and will

continue to be required, so that the antibiotics really bear only slightl on this particular problem.

Another very important aspect of preventive medicine is the reductio in the number of individuals who spread the organisms—carriers, i other words.

Dr. Miller, would you discuss the matter of carriers, their importanc and what we can do about it?

DR. MILLER: The problem of the carriers is still a serious one. A carrie is a healthy individual who harbors certain disease-producing bacteri and spreads them in the community. That is to say, a carrier does nc suffer from an infectious disease himself, but he infects other people– people with whom he comes in contact. Everyone has heard of "Typhoi Mary," the cook who became famous after she had caused at least te outbreaks of typhoid fever over a period of years and about fifty know cases of typhoid fever. Unfortunately these drugs are not much good i controlling carriers, for they do not rid typhoid carriers of the typhoi germs which they carry and spread about the community.

There is one other use of the antibiotics which should be mentioned They can be used to prevent an individual from coming down with disease after he has been exposed to it. The most successful example o such treatment has been obtained with the use of penicillin in preventin the development of gonorrhea.

The antibiotics are also able to prevent the development of infection of the middle ear and mastoid, which are really extensions of infectio from the throat or nose into the ear or mastoid bone. These complica tions used to occur frequently in children after streptococcus sore throat or scarlet fever. They often required operation. Today they are muc less frequent because the diseases which caused them can now be brough under control with penicillin.

Another important use of the antibiotics is in the field of surgery Surgeons used to fear the possibility of peritonitis developing whenev they had to operate on the large intestine. Of course, great advances i surgical methods have been made in the past decade. But, in addition, b giving suitable drugs to patients before and immediately after operation the surgeon is able to minimize the chance of infection developing at th site of an operation. The surgeon has also welcomed these drugs as means of preventing pneumonia, which sometimes developed in pa tients after major operations—particularly on old people. Pneumoni

was always a serious complication. In fact, any condition, such as apoplexy or a broken hip, which kept old people in bed for long periods of time would often set the stage for an attack of pneumonia. Pneumonia used to be called the "old man's friend," because it so often would put an end to lingering illness.

In fact, the antibiotics have eliminated so many infectious diseases as causes of death, not only in the old people but in people of all ages, that a great change is taking place in the kinds of diseases from which people are going to die. As more and more people reach the ages when cancer and the degenerative diseases are frequent, the incidence of these diseases will become increasingly important in medicine. For this reason emphasis in medical research is now shifting to the study of cancer and the diseases of the arteries and heart and kidneys which increase as the aging process progresses.

Now, just a word of caution. Dr. Smadel and Dr. McDermott both agree with me that these drugs should not be used indiscriminately, for the reasons which we have mentioned. They should be taken only on the advice of a physician and under his supervision. One of the many reasons why the antibiotics should be used only under a doctor's supervision is that, as we succeed in controlling the common and better-understood diseases such as we have mentioned, doctors now discover that their patients develop certain rarer types of infection more frequently. Some of these are not as yet well understood.

We can say then that the introduction of the wonder drugs has brought about a tremendous advance in the treatment of most of the infectious diseases. Penicillin has saved the lives of countless patients suffering from pneumonia and epidemic meningitis; it is a rapid and effective treatment for syphilis and gonorrhea. Streptomycin is of great help in treating tuberculosis, as Dr. McDermott has pointed out, and certain infections of the urinary tract. Aureomycin and chloromycetin, the most recent discoveries, are proving successful in the treatment of typhoid fever, brucellosis, and the rickettsial diseases which Dr. Smadel has investigated—typhus fever, scrub typhus, and Rocky Mountain spotted fever. We have as yet no drug for most of the virus infections such as polio, or infantile paralysis, influenza, and, the commonest of all, the common cold.

SOME OBSERVATIONS ON THE DEVELOPMENT OF RESISTANCE TO ANTIBIOTICS

By C. PHILLIP MILLER

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PENICILLIN

THE mode of action of penicillin has been the subject of much experimental study and a good deal of speculation. In spite of this, we do not yet understand how it works. We do know that it acts on bacterial cells only when they are in a state of active growth, *not* when they are in a resting state, and we know that it interferes in some fashion with the process of cell division. Dr. Gale at Cambridge University, working with Staphylococcus, for example, found that penicillin interferes with assimulation of glutamic acid by the bacterial cell; but there is reason to believe that this is not the complete explanation. It is quite possible that the mechanism of its action is not the same in all species of bacteria.

The remarkable effectiveness of penicillin in controlling infections caused by susceptible bacteria is well known. When penicillin first became available for clinical trial, its principal drawback was already known to be its rapid elimination by the kidneys. To overcome this disadvantage, it was at first administered continuously, either by intravenous or intramuscular drip, and later by frequent intramuscular injection. Great attention was given to the maintenance of a level of concentration in the blood sufficient to inhibit the growth of the microorganism concerned. This emphasis on blood levels was based on experience with the sulfonamide drugs, when it was important to follow the blood level not only to insure an adequate concentration of the drug but also to prevent its rising to a level which was toxic for the patient. The toxicity of the sulfa drugs fixed a ceiling above which it was unsafe to raise the concentration in the blood. In the case of penicillin, however, there is almost no limit to the amount of drug which can be safely given the average patient.

If one determines the concentration of penicillin in the blood after an intramuscular injection in a patient with normal kidney function, one finds that it rises steeply to a maximum and then falls rapidly. When the concentration necessary to inhibit bacterial growth in the test tube

vas found to be at a certain level, an attempt was made to keep the concentration of penicillin above that level as much of the time as possible by shortening the intervals between injections. It has only been recently discovered that a single large injection does this more effectively than two small injections. Nevertheless, one of the first reports by Tillett in 1944 on the treatment of pneumococcal pneumonia with penicillin showed that an interval as long as twelve hours between injections was satisfactory except in unusually severe infections. And it also has been shown that the interval between injections in mice could safely be lengthened if the dose were correspondingly increased.

Recently Eagle's work at the National Institutes of Health explains what is happening to the bacteria during the periods when the blood concentration is negligible. This study followed up and amplified an observation made a few years ago at Western Reserve University that bacteria do not resume multiplication immediately after they have been removed from penicillin. In other words, the inhibitory effect of penicillin on bacteria persists for some time after its removal, and the bacteria pass through a lag phase before they resume multiplication. If penicillin is added to an actively growing culture, for example, the bacteria stop multiplying and begin to die. But when the action of penicillin is stopped by the addition of a penicillin-destroying enzyme, they do not resume mulitplication at once but only after a period of several hours. These findings explain in part what is happening to bacteria during the periods when negligible quantities of penicillin are present in the blood of a patient.

Another factor which has been too much neglected since the introduction of the antibiotics is the role of the body's defense mechanism. When the bacterial population in the body is reduced, the white blood cells are busy doing what might be called a "mopping-up" operation. In our enthusiasm over the benefits of these antimicrobial agents we have tended to lose sight of the natural processes of recovery. We are apt to forget the host-parasite-drug relationship which is involved in an infection under treatment in which the defense mechanism of the patient has a great deal to do with recovery.

The development of bacterial resistance is a problem which has attracted a good deal of attention in the last few years because of its great theoretical interest and its practical importance. There is no doubt that a susceptible strain of bacteria can be made highly resistant to penicillin by growing it repeatedly in increasing concentrations of penicillin. We

were able, for instance, to raise the resistance of a strain of meningococcus about 20,000 fold during 147 subcultivations on agar containing increasing concentrations of the drug. It was also possible to develop resistant meningococcus in infected mice by giving subcurative doses of penicillin.

The explanation of this interesting phenomenon, the development of resistance to penicillin, has been supplied by the geneticist, Demerec, who showed that it is due to mutation. A large bacterial population is not homogeneous with respect to its sensitivity to penicillin, even though the whole population may have originated from a single bacterial cell. While almost all the members of such a population may be sensitive to a given concentration of penicillin, it may contain a very few individuals which are resistant to that concentration. If such a culture is planted onto media containing that concentration of penicillin, only the resistant individuals will be able to multiply. All the rest will be inhibited. Since the descendants of these resistant individuals are also resistant to this higher concentration, the resistance is a hereditary trait not possessed by their ancestors and must, therefore, be the result of mutation. The proportion of such resistant mutants in a bacterial population is usually in the neighborhood of one in a billion.

It is of particular importance to clinicians that each mutation increases the resistance of the strain very little, so repeated subcultivations at gradually increasing concentrations of penicillin are required to raise the resistance to a high level. This is one of the reasons why the development of penicillin resistance is not a serious problem in treating patients. In the treatment of any given infection, the bacteria do not have time to develop resistance because the bacterial population is too quickly reduced by penicillin. Another reason is that penicillin is usually administered in much larger doses than is actually necessary to bring an infection under control.

STREPTOMYCIN

The mode of action of streptomycin is not yet understood despite a good deal of experimental work. We do know certain things about its action—principally, that it interrupts the process of cell division, probably by interfering with some enzyme system essential to that process.

The action of streptomycin in the patient differs from that of penicillin in being toxic for the kidneys and for the auditory nerve, particularly the portion having to do with maintenance of balance. While some of the toxic effect in the earlier preparations was due to impurities, nevertheless

a certain amount of this property is retained by preparations of the highest degree of purity, showing that it is a characteristic of the streptomycin molecule itself. Tendency to damage the auditory nerve has been somewhat reduced by hydrogenation, which adds two hydrogen atoms to the molecule producing what is known as dihydrostreptomycin.

When streptomycin is given by mouth, there is practically no absorption from the gastrointestinal tract or secretion into it from the blood stream. In other words, for all practical purposes there is no transport through the wall of the stomach or intestine. This accounts for the success of oral administration of streptomycin in reducing the bacterial population of the intestinal tract, a procedure which the surgeons have found very useful as a prophylactic measure before operations on the large bowel. Unfortunately, bacteria develop resistance very rapidly to streptomycin, and in a few days the normal flora of the bowel is replaced by a streptomycin-resistant population, so the prophylactic oral administration of streptomycin should not be begun more than two days before operation.

The development of resistance to streptomycin is a much more interesting phenomenon from the academic standpoint than the development of resistance to penicillin, and a more serious problem to the clinician. It occurs much more rapidly and reaches a very much higher level. Only two or three subcultivations on media containing streptomycin are necessary for susceptible bacteria to acquire sufficient resistance to permit them to grow abundantly on very high concentrations of the drug. As in the case of penicillin resistance, this increase in streptomycin resistance is due to the appearance of streptomycin-resistant mutants in the normal bacterial population; but these mutants are of two types, one of which is resistant in the ordinary way and the other dependent on streptomycin for growth.

The streptomycin-resistant bacteria will multiply in the presence of high concentrations of streptomycin and, when injected into mice, will produce infections which cause death in spite of any amount of treatment with the drug. The streptomycin-dependent bacteria will multiply *only* in the presence of streptomycin. When these dependent bacteria are inoculated into mice, no infection develops, and the mice survive because the bacteria require streptomycin for their growth even in the body of the animal. However, when mice are infected with these dependent bacteria and the animals are treated with streptomycin, infection develops and causes death, because the multiplication of the depend-

ent bacteria has been promoted by the streptomycin. This is a complete reversal of the customary action of an antibiotic. Fortunately, these streptomycin-dependent bacteria are rarely if ever a complicating factor in the treatment of human disease with streptomycin.

We have not found any substance which will substitute for streptomycin in supporting the growth of these dependent bacteria, although we have tried a number of streptomycin derivatives—streptamine, streptidine, streptobiosamine, as well as streptomycin which has been inactivated by cysteine hydrochloride or hydroxylamine. It is surprising that utilization of streptomycin by these streptomycin-requiring organisms cannot be demonstrated experimentally. The method of determining streptomycin concentration is admittedly inexact, but it should detect a loss of any considerable amount of streptomycin from broth in which these organisms have grown, and one would expect them to consume a detectable amount considering the high concentrations they require for growth.

The rapid development of streptomycin resistance presents serious limitations on the usefulness of this antibiotic in the treatment of patients. It is well recognized, for instance, that unless an infection of the urinary tract can be successfully controlled within two or three days, further treatment is useless because the infecting bacteria will have become completely resistant by that time. In the case of tuberculosis, resistance develops much more slowly, because the tubercle bacillus multiplies more slowly. Nevertheless, the development of streptomycin resistance is recognized as a serious problem and the cause of great concern to those engaged in the treatment of that disease.

The question has naturally arisen whether streptomycin-dependent bacteria occur in nature or whether they develop only under the artificial conditions of laboratory experiments—in other words, whether they are laboratory freaks. This question was investigated by treating normal rabbits and mice with large doses of streptomycin and making periodic cultures of the pharynx and large bowel on streptomycin media. After a week both streptomycin-resistant and streptomycin-dependent mutants were recovered from these animals.

We also made throat cultures on patients who were being treated with streptomycin. It was found that streptomycin-resistant bacteria, including a small proportion of streptomycin-dependent bacteria, could be recovered from the throats of those who were being treated with streptomycin.

Fortunately, organisms which have developed resistance to one antibiotic are susceptible to the others. This can easily be shown with meningococcus, which is sensitive to both streptomycin and penicillin. The growth of a penicillin-resistant meningococcus, for example, is inhibited by streptomycin just as effectively as its susceptible parent-strain, and a streptomycin-resistant meningococcus is inhibited even more than its parent-strain. In other words, a streptomycin-resistant mutant is somewhat more sensitive to penicillin than the normal strain from which it was derived. This reciprocal effect can also be demonstrated with the sulfonamide drugs.

It is quite rational, therefore, to administer penicillin and sulfadiazine for the treatment of infections with bacteria which are not very sensitive to either one alone. And in the case of infections which call for streptomycin therapy the addition of one of the sulfonamides may not only enhance the chemotherapeutic effect but will retard the development of resistance. This is understandable if one considers the genetic changes involved in the development of resistance. If mutation to streptomycin-resistance occurs in one bacterial cell out of approximately a billion, and resistance to one of the sulfa drugs, say, sulfadiazine, occurs at about the same rate, the chance that a double mutation will occur (one which will be resistant to both drugs) is the arithmetic product of these two figures: that is, one in a billion billion, since $10^9 \times 10^9 = 10^{18}$.

AUREOMYCIN AND CHLOROMYCETIN

Aureomycin is produced by *Streptomyces aureofaciens* and is active against a wide variety of bacterial species and also against certain of the rickettsiae and possibly a few of the viruses. This makes it a very valuable addition to our stock of antibiotics. One great advantage is that it can be administered by mouth. It is reasonably nontoxic, although in therapeutic doses it may cause mild gastrointestinal disturbances in some patients—nausea, occasionally vomiting, and diarrhea. This is seldom a serious handicap.

Besides being active against many of the infections susceptible to penicillin—that is, those caused by the Gram positive cocci and those susceptible to streptomycin—it is effective in the treatment of brucellosis, typhoid fever, tularemia, typhus fever and Rocky Mountain spotted fever.

Several workers have investigated the development of bacterial resistance to aureomycin. It is clear that resistance does not deveolp rapidly, as it does to streptomycin. Demerec believes that it follows the pattern

of penicillin but admits that experimentation is made difficult by the fact that aureomycin loses its potency during incubation at 37° C., so that organisms whose growth had been inhibited on agar media are able to resume multiplication after the concentration has been reduced by the deterioration of the aureomycin during prolonged incubation.

Chloromycetin (Chloramphenicol) has properties quite similar to aureomycin. It, too, can be given by mouth and is active against the same diseases. Chloromycetin is unique in being the first antibiotic to be prepared synthetically on a large scale, and a good deal of the material now available is made in that way.

There seems to be disagreement about the relative merits of chloromycetin and aureomycin in the treatment of such diseases as brucellosis, but the differences are not very sharp, and the two drugs are about equally effective.

Intelligent use of the antibiotics depends upon accuracy of diagnosis. This is one of the many reasons why these drugs should be taken only on the recommendation of a physician and under his supervision. The indiscriminate use of these drugs has increased the difficulty of arriving at a bacteriological diagnosis which is made by culturing the causative bacteria from the patient. This procedure becomes very difficult if the patient has already taken sufficient antibiotic to interfere with the growth of the bacteria in the test tube. One of the great needs in the field of infectious diseases today is improvement in our methods of bacteriological diagnosis.

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